World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

# SYNTHESIS OF PHENYTOIN BY GREEN CHEMISTRY APPROACH

**Amir, Ashfaque Alam, Fauwaz Aftab, Gulam Nabi, Sadre Alam, Devendra Dhariwal* and Jagdish Chandra Rathi**

NRI Institute of Pharmaceutical Sciences, Sajjan Singh Nagar, Opposite Patel Nagar, Raisen Road Bhopal, MP, 462022.

***Corresponding Author: Devendra Dhariwal**
NRI Institute of Pharmaceutical Sciences, Sajjan Singh Nagar, Opposite Patel Nagar, Raisen Road Bhopal, MP, 462022.

**Article Received on 20/02/2023** **Article Revised on 11/03/2023** **Article Accepted on 01/04/2023**

**ABSTRACT**
Green chemistry is the design of chemical products and process that eliminates the use and generation of hazardous substances. Using green solvent, like water, synthesis of biologically active moiety with high percentage yield as well as purity. The Percentage yield of Phenytoin obtained by Green Chemistry Approach is 95.95% whereas Conventional/Traditional method produces only 89.83% phenytoin constant concentration of all organic reagents. Hence we concluded that Green chemistry approach is environment friendly.

**KEYWORD:** Green chemistry, Phenytoin, Conventional/Traditional method.

## INTRODUCTION

Green Chemistry is defined as invention, design, development and application of chemical products and processes to reduce or to eliminate the use and generation of substances hazardous to human health and environment. Green chemistry is the design of chemical products and process that eliminates the use and generation of hazardous substances. Using green solvent, like water, synthesis of biologically active moiety with high percentage yield as well as purity is the one of objective of green chemistry.

- Since its introduction about 80 years ago, phenytoin has not only been established as an effective anti-epileptic, but has also been investigated for several other indications such as bipolar disorder, retina protection, and wound healing.
- Both parenteral and oral formulations of phenytoin are available on the market.
- It was the 221st most commonly prescribed medication in the United States, with more than two million prescriptions.
- Common side effects include nausea, stomach pain, loss of appetite, poor coordination, increased hair growth, and enlargement of the gums. Potentially serious side effects include sleepiness, self harm, liver problems, bone marrow suppression, low blood pressure, and toxic epidermal necrolysis.

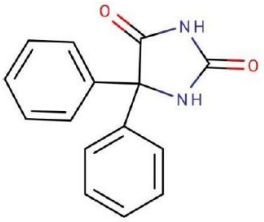
### Principles of green chemistry

It is better to prevent waste than to treat or clean up waste after it is formed. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. Wherever practicable synthetic methodologies should be designed to use and generate substances that pose little or no toxicity to human health and the environment. Chemical products should be designed to preserve efficacy of function while reducing toxicity. The use of auxiliary substances (e.g. solvents, separation agents etc.) should be made unnecessary wherever possible and, innocuous when used. Energy requirements should berecognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure. Substances and the forms of the substance used in chemical reaction should be chosen so as to minimize the potential of chemical accidents, including releases, explosions, and fires.

### Green approaches in organic synthesis

The concept of green chemistry introduced the environmentally benign synthetic protocols for the synthesis of heterocycles that has had a significant impact in many fields, such as the use of green solvents, solvent-free synthesis, sustainable catalytic materials, reduced energy consumption, improved atom economy, optimized reaction yields, the use of alternative energy sources, the introduction of multicomponent reactions ionic liquids and the design of high- efficiency and time-saving reactions that work at ambient temperatures. Pollution and an increase in energy demands prompted the design of novel synthetic protocols to fulfill the requirements of green and sustainable chemistry to promote the synthesis of organic products in an ecofriendly environment.

**Phenytoin**

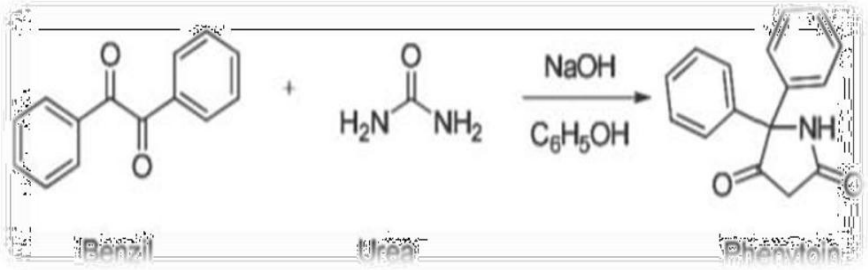


**IUPAC Name**

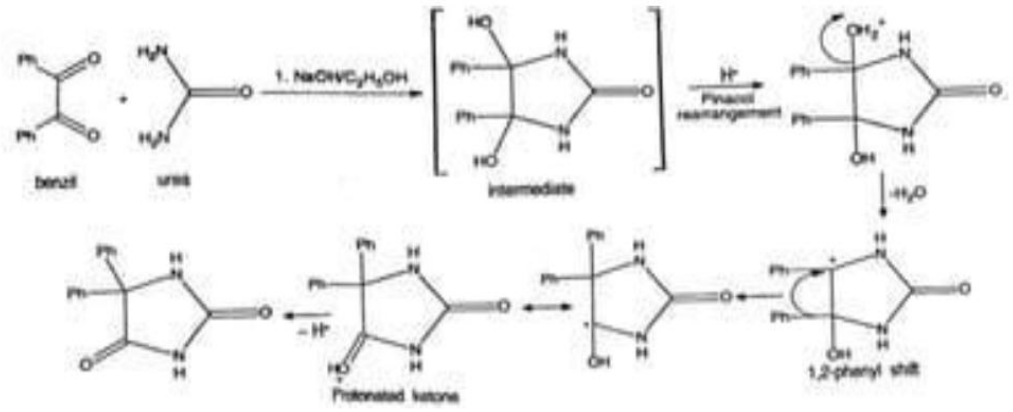
5, 5-Diaphenylhydantoin

**Chemical Formula**

$C_{15}H_{12}N_2O$




**Preparation of phenytoin by traditional method from Benzil and Urea reaction Mechanism**




**Procedure by traditional method**

- Place 5.0g of benzil, 3.0 g of urea, 15 ml of aqueous sodium hydroxide solution (30%) and 75 ml of ethanol in a round bottomed flask of 100 ml capacity.
- Set up a reflux condenser with the flask and boil using an electric heating mantle for atleast 2 hrs.
- Cool it at room temperature.
- And, pour the reaction mixture into 125 ml of water and mix carefully.
- Allow the reaction mixture to stand for 15 min.
- And then filter the product under suction to remove an insoluble by-product.
- Render the filtrate strongly acidic with concentrated hydrochloric acid.
- And then cool in ice-water.
- And immediately filter off the precipitated product under suction.
- Recrystallise at least once from Hydrochloric Acid to obtain about 2.8 g (44%) of pure 5, 5-diphenylhydantoin, Melting Point 297-298 °C.

**Calculation of traditional method**

Molecular Weight of Benzil = 210.23 gm/M
Molecular Weight Phenytoin = 252.26 gm/M
Weight Taken Of Benzil = 5 gm
Practical Yield= 5.3 gm

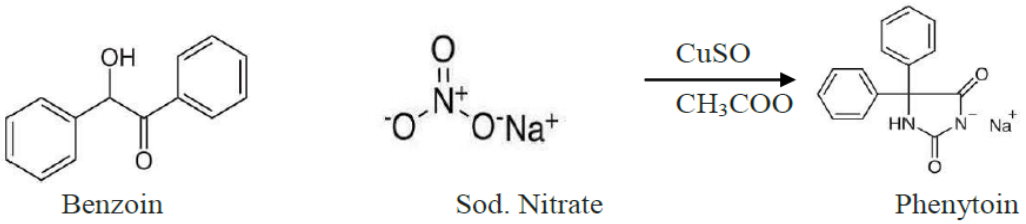
$$\text{Theoretical Yield} = \frac{\text{Molecular Weight Of Phenytoin} \times \text{Weight Of Benzil taken}}{\text{Molecular Weight of Benzil}}$$

$$= \frac{252.26\ \text{gm/M} \times 5\text{gm}}{210.23\text{gm/M}} = 5.9\ \text{gm}$$

Percentage Yield = Practical Yield / Theoretical Yield × 100 %

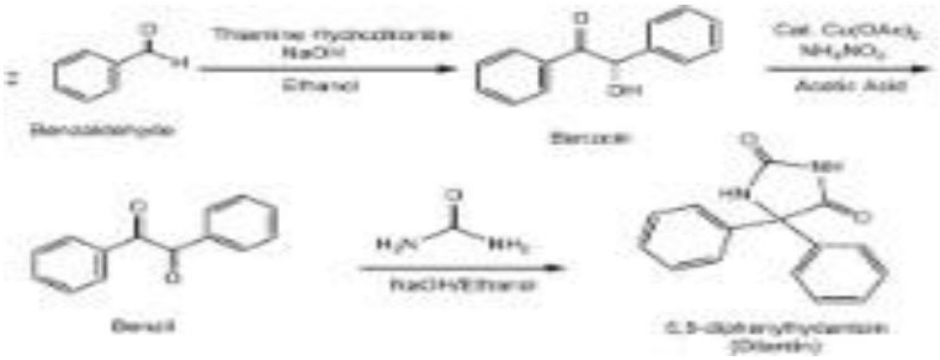
Percentage Yield = 5.3 gm / 5.9 gm × 100%
Percentage Yield = 89.3%

**Preparation of phenytoin by green chemistry approachfrom benzoin and sodium nitrate**
**Reaction**




Benzoin Sod. Nitrate Phenytoin

**Mechanism**



**Procedure by green chemistry approach**

- In the round Bottom Flask Place 5.0g of benzoin, 12.5ml of acetic acid and 2 g sodium nitrate were taken.
- The 2% copper sulfate was prepared separately and 2.5 ml was added to RBF.
- The mixture in RBF was stirred in circumfluence for 1.5h.
- The mixture was cooled to 50-60$^0$.
- And pour the reaction mixture into 125 ml of water and mix carefully.
- Allow the reaction mixture to stand for 15 min.
- And then filter the product under suction to remove an insoluble by-product.
- And immediately filter off the precipitated product under suction.
- Recrystallise at least once from Acetic Acid to obtain 5, 5-diphenylhydantoin.

**Calculation of green chemistry approach**

Molecular Weight of Benzoin = 212.24 gm/M
Molecular Weight Phenytoin = 252.26 gm/M
Weight Taken of Benzoin = 5 gm
Practical Yield= 5.7 gm

$$\text{Theoretical Yield} = \frac{\text{Molecular Weight Of Phenytoin} \times \text{Weight Of Benzoin taken}}{\text{Molecular Weight of Benzoin}}$$

$$= \frac{252.26\ \text{gm/M} \times 5\text{gm}}{212.24\text{gm/M}} = 5.94\ \text{gm}$$

Percentage Yield = Practical Yield / Theoretical Yield × 100 %

Percentage Yield = 5.7 gm / 5.94 gm × 100%
Percentage Yield = 95.95 %

**RESULT AND DISCUSSION**

| Sr. No | Method | % Yield |
|---|---|---|
| 1. | Synthesis of Phenytoin By Traditional Method. | 89.83% |
| 2. | Synthesis of Phenytoin By Green Chemistry Approach. | 95.95% |

The Percentage yield of Phenytoin obtained by Green Chemistry Approach is 95.95% whereas Conventional/Traditional method produces only 89.83% phenytoin constant concentration of all organic reagents.

Hence we concluded that Green chemistry approach is environment friendly.

**CONCLUSION**

Phenytoin is synthesized by application of principle of green chemistry with high purity profile as well as having safety by omitting the use of ethanol. Water a green solvent is used instead of ethanol in synthesis of phenytoin .There is reduction in time and ultimately cost as compare to conventional procedure of synthesis of phenytoin. Thus we conclude that the synthesized

compound have potential in the green chemistry.

**REFERENCES**


1. Kidwai M, Green Chemistry in India; Pure Appl Chem, 2001; 73: 1261-1263.
2. Bell G S and Sander J, Seizure, 2002; 11: 306-314.
3. Tripathi K D, Essentials of Medical Pharmacology; Jaypee Publications: New Delhi, 2003; 495-498.
4. Bigge C and Boxer P, Annu Rep Med Chem, 1994; 29: 13-22.
5. Wong M G, Defina J A and Andrews P R, J Med Chem, 1986; 29: 562-572.
6. Furniss B, Hannaford J, Smith P W G and Tatchell A R, Vogel's Textbook of Practical Organic Chemistry; Dorling Kindersley: New Delhi, 2008; 5: 1153.
7. Vogel H, Drug discovery and Evaluation Pharmacological Assays: Springer Publication: Berlin, 2002; 422.
8. Achliya G S, Wadodkar G S and Dorle A K, J Ethnopharmacolo, 2004; 94(1): 77-83.
9. Nguelefack T B and Astamo A D, J Ethnopharmacolo, 2006; 106: 70-75